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The Cost-Effectiveness of Atypicals in the UK

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ABSTRACT

Background: In 2002, the National Institute for Health and Clinical Excellence (NICE), recommended atypical antipsychotics over conventional ones for first-line schizophrenia treatment, based on their lower risk of extrapyramidal symptoms.

Objective: To estimate the incremental cost-effectiveness of atypical relative to conventional antipsychotics for the treatment of schizophrenia in the UK.

Methods: A discrete event simulation (DES) model was adopted to reflect the treatment of schizophrenia in the UK. The model estimates symptoms (using the Positive and Negative Symptom Score [PANSS]), psychiatrist visits, pharmacological treatment and treatment location, number and duration of psychotic relapses, level of compliance, quality-adjusted life-years (QALYs), and side effects over a 5-year time period. Probabilistic sensitivity analyses were carried out. Following NICE's "atypical" recommendation, the cost-effectiveness of atypical versus conventional antipsychotics was estimated in a scenario analysis, assuming both groups differ only in side-effect profile.

Results: When comparing conventional and atypical antipsychotics, the model predicts that the latter would decrease 5-year costs by £1633 per patient and result in a QALY gain of 0.101. The probabilistic sensitivity analysis suggests these results are robust. The sensitivity analyses indicate that incremental costs and effects are most sensitive to the differential efficacy of atypicals and conventionals, as measured by PANSS. When it is assumed that the only differences between atypicals and conventionals are found in side-effect profiles, the incremental cost-effectiveness ratio of the atypicals is £45,000 per QALY gained.

Conclusion: According to this DES model for schizophrenia, atypical antipsychotics are cost-effective compared to the conventional antipsychotics. The assumptions used in the model need further validation through large naturalistic based studies with reasonable follow-up to determine the real-life differences between atypicals and conventional antipsychotics.

Keywords: cost-effectiveness analysis, discrete event simulation, modeling, probabilistic multivariate sensitivity analyses, schizophrenia, UK.

Introduction

Schizophrenia is a chronic disease with no definitive cure. The prevalence of the condition is estimated at between 0.2% and 1% in the general population [1,2]. Schizophrenia typically starts at a young age with considerable impact on the patients and their social system. As a result, the societal costs of schizophrenia are substantial. According to Mangalore and Knapp, the estimated total societal cost of schizophrenia in the UK was 6.7 billion pounds in 2004 to 2005 [3].

The National Institute for Health and Clinical Excellence (NICE) recommends that atypical antipsychotics should be considered first-line treatment for newly diagnosed schizophrenia patients, particularly when full discussion between clinician and patient is not possible [1,4]. This recommendation is based on the lower potential risk of extrapyramidal symptoms (EPS) on atypical antipsychotics than on conventional ones. The guidance recognizes that patients who are currently successfully treated with a conventional need not be switched to an atypical antipsychotic when symptom control is adequate and side effects are acceptable. The present study addresses the cost-effectiveness of the use of atypical antipsychotics in the early treatment of schizophrenia.

Reliable data of the long-term impact of schizophrenia and its treatment are scarce, both in terms of clinical as well as economic outcomes. Additionally such data are often of poor quality and difficult to generalize among a broad population [5]. This hampers making well-informed decisions concerning reimbursement and treatment guidelines. A health economic model, which consolidates the available evidence in a structured manner, may, however, be able to help gain insight into the different mechanisms which

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influence treatment outcomes. While the outcomes of such a model should be treated with caution [5], they can still be of great value in serving as a starting point for further research and discussion. It may be argued that the lower the quality of the evidence is, the more closely a model should reflect clinical practice and rely on explicit assumptions and interdependencies, so that the impact of each can be individually tested and reviewed. Furthermore, this approach potentially makes the model more suitable for the inclusion of expert opinion to complement the published literature, as the level of abstraction is reduced to a minimum. This realization, along with the highly heterogeneous and time-dependent nature of the illness and its progression, makes schizophrenia a highly suitable candidate for discrete event simulation (DES) [6,7]. DES models allow for the simulation of individual patients and they are highly flexible in terms of their time frame, as well as the inclusion of a large number of interdependencies with respect to individual patient characteristics and their treatment histories.

The current article aims to provide insight and understanding regarding the clinical and economic effects of the treatment of schizophrenia, using a nonproduct-specific DES model which represents the use of pharmacological agents in day-to-day clinical practice in the UK. The objective was to assess the cost-utility of atypical versus conventional antipsychotics based on their respective market shares in the UK treatment setting.

Methods

Perspective

The analysis of costs is restricted to health and social care costs borne by the NHS and social care trusts. Hence only the direct costs of medication, psychiatric visits, and costs associated with residing in specific treatment locations (e.g., community treatment, staffed hostel, or hospital) are included. In accordance with NICE guidelines, costs and effects are discounted at a rate of 3.5% [8]. Indirect costs are not included in the analysis because little research has been carried out on the impact of antipsychotic treatment on indirect costs and it is unclear whether differences in indirect costs between different treatments are to be expected. In any case, indirect costs are not expected to be higher on atypicals than on conventionals [9,10].

Data Sources and Discrete Event Model

Previous versions of the DES model used for this analysis have been described in detail elsewhere [11–13]. Where possible, parameter estimates were updated based on published literature or with information from secondary database analyses (from the ongoing University Medical Center Utrecht database of schizophrenia patients). The DES model was programmed using Extend software (Imagine That Inc., San Jose, CA). The model describes the course of treated schizophrenia over 5 years. Schizophrenia is a chronic disease and therefore theoretically a lifetime time horizon should be considered when modeling schizophrenia. Nevertheless, because of the lack of long-term data on the course of schizophrenia, a 5-year time horizon was chosen. This time horizon is sufficient to capture the relevant health and economic consequences of the treatments under comparison, because patients typically switch quite frequently between antipsychotics [14], and both treatment arms have the same second-, third-, and fourth-line treatment.

Comparisons Made

The treatment strategies that are compared using this DES model are outlined in Figure 1. When the patient enters the model or switches treatment, an antipsychotic is selected based on UK market share data (IMS November 2005) [15] in order to approximate treatment selection in clinical practice. Little data are available about the distribution of the different drugs at different stages of treatment, so it is assumed that this distribution is the same throughout. The choice of second, third, and fourth treatment has little impact on incremental results because these distributions are the same in both treatment arms. Up to three treatment switches are allowed in the 5-year model (Fig. 1). Following expert opinion and the NICE treatment guidelines, all patients switch to clozapine after the third treatment [16].

Model Structure

The development of the current DES model was initiated in 2000. Initially, model inputs were, to a large extent, based on expert opinion. Nevertheless, over time the model was increasingly populated (and validated) using published data or secondary database analysis. Previous versions of the DES model used for this analysis have been described in detail elsewhere [11–13]. Structural changes to the model incorporate the possibility for probabilistic sensitivity analyses, as well as additional outcome measures, partial compliance, and three instead of two treatment switches.

Patients enter the model while suffering an episode for which the care of a psychiatrist is sought. It is assumed the patient is presenting early on in the course of the illness, but it is not the first episode of psychosis (as distinct from first episode of schizophrenia), because the diagnosis of chronic schizophrenia cannot be made based on a single psychosis. Therefore, patients may not be treatment naïve. Figure 2 provides a graphical representation of a hypothetical patient history. During each visit, the next visit is planned and the patient's location of care, treatment, and compliance are re-evaluated. The variables included in the

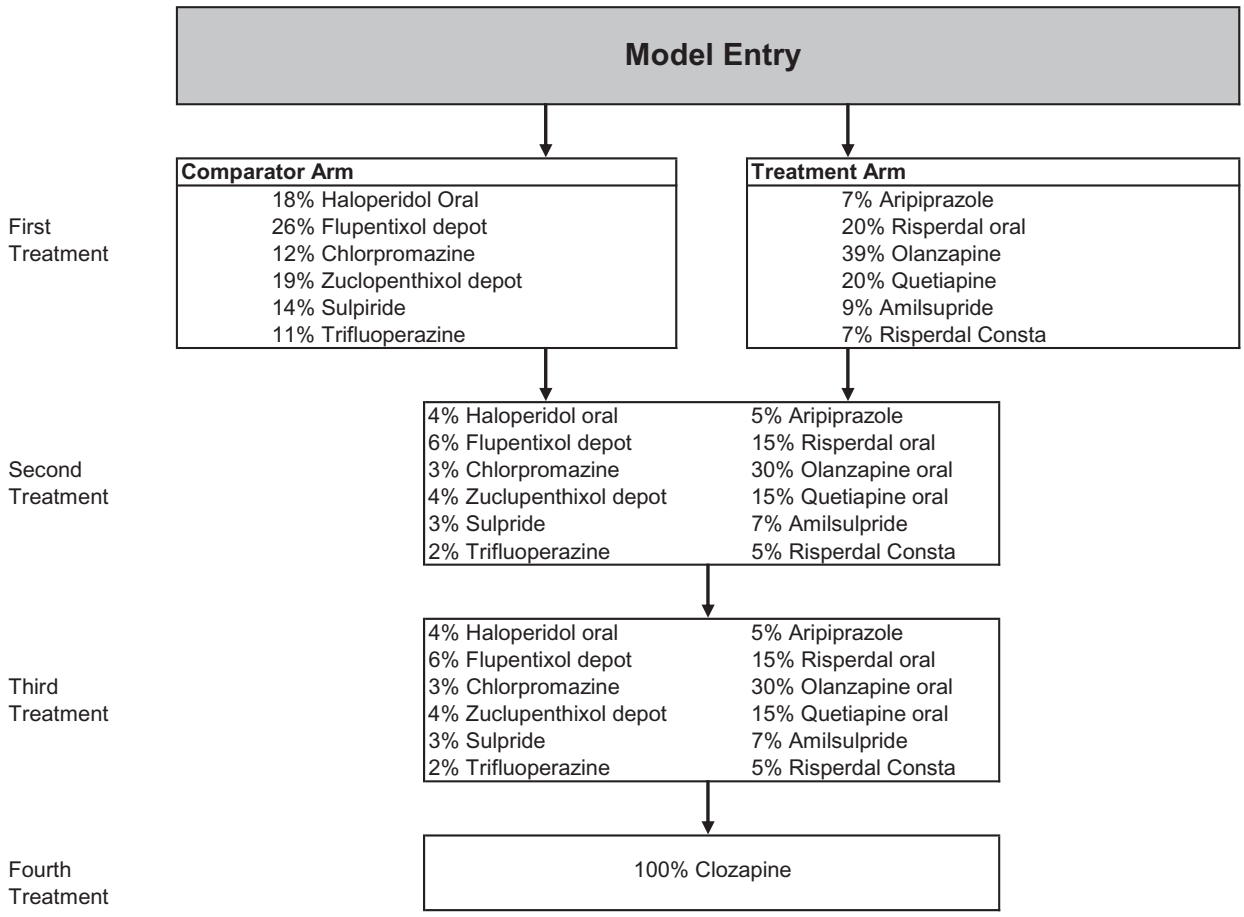

Figure 1 Overview of modeled pharmaceutical treatment strategies and the treatments probabilities in the first, second, third, and fourth treatment after model entry, based on UK market shares [15].

model are either fixed (patient characteristics/attributes) or time dependent.

Fixed Patient Attributes

Simulation of individual patient histories starts with selecting a number of attributes from a set of prespecified probability distributions:

1. Patient profile (which determines whether a patient recovers fully or partially between relapses in terms of the symptom score—38% of patients recover fully, 62% partially) [17];
2. The severity of illness of the patient (mild 10%, medium 80%, or severe 10%) [11];
3. Social and environmental factors (SEF: a random score between 0 and 100 which represents a patient's informal care network (as previously described [11]); and
4. Whether a patient will suffer from side effects when put on a specific medication (see Table 1). Once the time-independent attributes are assigned to a patient, the model simulates disease progression based on a number of interdependent time-dependent variables.

Side-effect incidence rates were calculated by multiplying the incidence of the relevant side effects on olanzapine (for EPS [18], tardive dyskinesia [19], somnolence [20], weight gain [>7% of initial body weight], [21] and diabetes [22]) by the relative risk reported in the Cochrane reviews of the various antipsychotics [23–34]. This approach was taken because little directly comparative data are available. By anchoring side effects for the other treatments on olanzapine data and using relative risks, some of the differences in trial design (such as dosing, length of trial, etc.), which make it difficult to use the raw data on which these relative risks were based, become less relevant.

Time-Dependent Variables

After these fixed attributes are assigned to a patient, the model simulates disease progression based on a number of interacting time-dependent variables. The two major time-dependent variables are the patient's health state at a certain moment (whether the patient is in relapse or is in between relapses) and the result of reassessment of medication and treatment location during psychiatrist visits. A patient's health state influ-

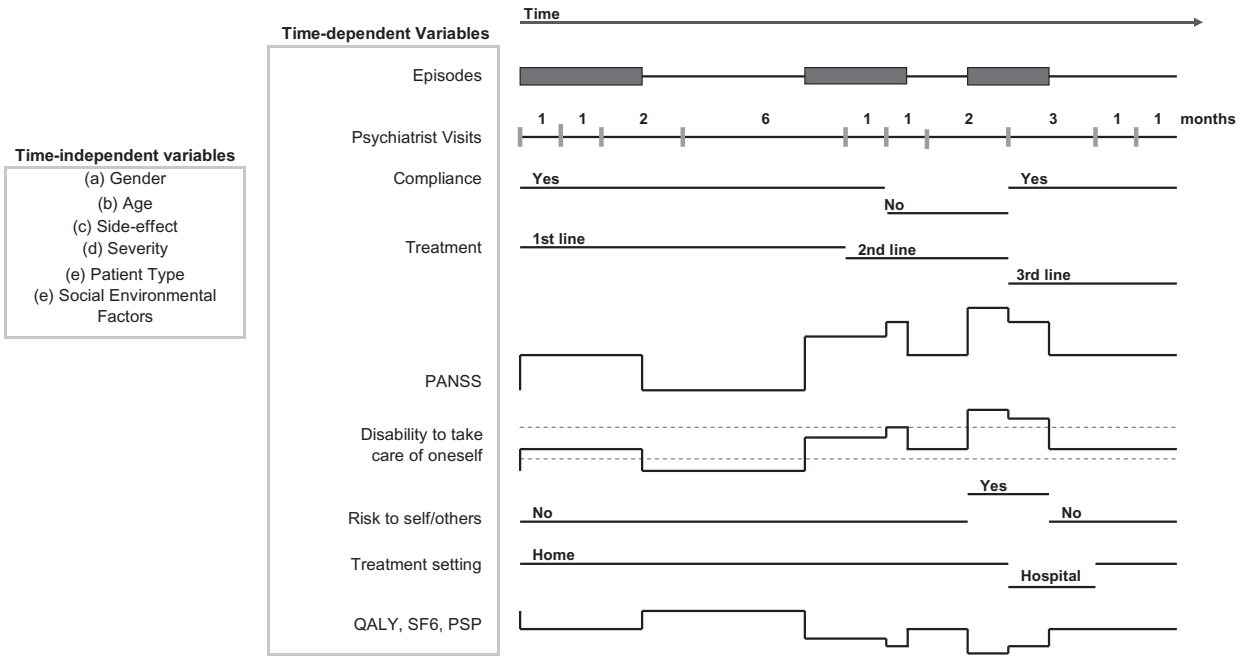

Figure 2 Example of patient history from time of entering model during relapse at visit to psychiatrist. QALY, quality-adjusted life-year; PSP, personal and social performance scale; SF6, short form 6 mental health component; PANSS, Positive and Negative Symptom Score.

ences the PANSS score which is associated with changes in quality-adjusted life-years (QALYs) [35]. Other time-dependent variables such as the level of compliance (fully, partially, or noncompliant), the risk to harm self and/or others, and the ability of a patient to care for him- or herself are dependent on a patient's PANSS score. The treatment characteristics (i.e., treatment and location) are determined during the psychiatric visits, based on the various interdependencies between the time-dependent and time-independent variables. In the following section, these interdependencies will be briefly elaborated upon.

Psychiatric Visits

Upon model entry, the simulated patient visits a psychiatrist. During each visit to the psychiatrist, the choice of treatment location and medication is evaluated. Psychiatrist visits in the model are scheduled more frequently after a treatment switch or hospitalization (when the frequency is once a month), and less frequently in times when a patient is stable when the frequency is one visit every 6 months.

Medication

The decision to switch to another medication regime depends on whether or not the patient is in relapse while on the current medication. Nevertheless, even if the patients do not suffer from a relapse, a medication change can be prescribed because of the occurrence of a side effect [4]. The probabilities which are being used to determine the medication to which a patient is transferred are specified in Table 1, be it that patients will not be prescribed the same medication twice.

Treatment Location

In clinical practice, patients can be treated in a wide variety of settings. For modeling purposes, this was simplified down to four treatment settings: regular or intensive community care (with one nurse visit every fortnight or two nurse visits every week, respectively), in a staffed hostel (group living accommodations with some staff on site), or in a hospital. These locations were selected based on expert opinion to capture the main locations where the majority of patients with schizophrenia can be found. The treatment location decision depends on whether the patient presents an actual risk to him/herself or to society and whether the patient can take care of him/herself. The probability of presenting a risk was based on a logistic regression analysis specifying the association between risk to self and others, and PANSS in long-term cohort data from the University Medical Center Utrecht, The Netherlands, using a logistic regression model [36]. Additionally, because experts indicated that symptoms were not the only driver, another random score was included, called social and environmental factor (SEF), reflecting all other factors influencing the patients' location decision that are not linked to symptoms, such as whether patient lives at home, has a job, etc. In the model, patients with a high PANSS and/or a high SEF score are assumed to have difficulties taking care of themselves modeled using the disability to care index (DCI).

Table 1 Overview quantified model parameters

Probability of side effects	EPS (%) [18]	Tardive dyskinesia (%) [19]	Sedation/Somnolence (%) [20]	Weight gain (%) [21]	Diabetes (%) [22]	Agranulocytosis (%) [83]	
Low-potency conventionals (chlorpromazine, sulpiride) [23,24]	32.70	3.50	48.90	10.00	0.50	0.00	
High-potency conventionals (others) [25,26]	58.00	5.40	48.90	10.00	0.50	0.00	
Aripiprazole [27]	23.90	0.80	26.20	20.50	0.60	0.00	
Amisulpride [28]	32.70	1.50	27.30	13.50	0.50	0.00	
Risperidone [29]	27.30	0.70	27.30	19.30	0.50	0.00	
Olanzapine [31]	15.50	0.50	29.70	41.00	1.00	0.00	
Quetiapine [32]	19.90	0.70	55.50	32.50	0.90	0.00	
Clozapine [33,34]	14.60	0.00	45.30	57.80	1.60	1.00	
Probability to switch treatment because of side effect	70	90	35	50	90	100	Exp. Op.

Compliance probabilities between relapses	Conventional oral	Conventional depot	Oral atypical agents	Long-acting risperidone	Exp. op. [52–58]
Community treatment	0.600	0.80	0.650	0.850	
Intense community treatment	0.750	0.95	0.800	0.990	
Sheltered living	0.650	0.85	0.700	0.900	
Hospital/Institute	0.800	0.95	0.850	0.990	

Patients who present risk from: To:	Community care	Intense community care	Sheltered living	Hospital	Exp op.
Probabilities to switch care setting					
Community treatment	0.05	0.00	0.00	0.00	
Intense community treatment	0.15	0.20	0.20	0.00	
Sheltered living	0.00	0.00	0.10	0.00	
Hospital	0.80	0.80	0.70	1.00	
Patients who can take care of themselves well/moderately/not					Expert opinion
Community treatment	0.98/0.70/0.10	0.90/0.05/0.00	0.30/0.05/0.00	0.80/0.75/0.05	
Intense community treatment	0.02/0.10/0.10	0.10/0.85/0.50	0.00/0.00/0.00	0.10/0.10/0.20	
Sheltered living	0.00/0.10/0.10	0.00/0.00/0.00	0.70/0.90/0.15	0.10/0.15/0.12	
Hospital	0.00/0.10/0.60	0.00/0.10/0.50	0.00/0.05/0.85	0.00/0.00/0.63	

Total recovery (partial recovery)		Nonsevere patients	Medium-severe patients	Very severe patients	
Positive and Negative Symptom Score (PANSS) and duration of (time between) relapses per patient profile (partial recovery patients in brackets)					
PANSS relapse	No treatment	68 (77)	94 (81)	111 (86)	[26,46,70]
	Conventional drugs	60 (68)	83 (72)	99 (77)	
	Atypical drugs	56 (64)	78 (67)	92 (71)	
PANSS between relapses	No treatment	52 (49)	52 (52)	52 (56)	[26,46,70]
	Conventional drugs	52 (40)	52 (43)	52 (47)	
	Atypical drugs	49 (36)	49 (38)	49 (41)	
Time between relapses (months)	Conventional drugs	20.2 (17.2)	18.4 (15.6)	16.5 (14.0)	[26,39,42,44]
	Atypical drugs	22.5 (19.2)	20.5 (17.4)	18.4 (15.7)	
	Partially noncompliant	10.1 (8.6)	9.2 (7.8)	8.3 (7.0)	
	Noncompliant	6.1 (5.2)	5.5 (4.7)	5.0 (4.2))	
Duration of relapse full (partial) recovery (in years)		0.18 (0.9)	0.46 (1.0)	0.66 (1.12)	Exp. Op.

The latter variable depends on PANSS, SEF, and alpha weight. The alpha weight represents the weight of PANSS in the DCI. If the weight of PANSS in the DCI is high, the difference in PANSS reduction between conventionals and atypicals will have a stronger impact on the hospitalization decision (see Appendix A) [11]. If the patient presents a risk or is unable to care for himself, the probability of going to (or staying at) the more intensive care settings (like hospital) is high. If the opposite applies, patients may be sent home, or to a less intensive care setting (like a staffed hostel). The transition probabilities are presented in Table 1. For instance, a patient who cannot take care of him/herself and is located in a hospital has a 63% chance to remain in the hospital. The latter is not 100% because experts indicated that availability of services is limited. The average duration of hospitalization for schizophrenia (ICD code F20) is 40 days, based on hospital episode statistics from the Department of Health [37].

Table 2 Overview of considered antipsychotics, their dose, and the corresponding acquisition costs

Atypicals	Daily dose (mg)	Annual costs	Conventionals	Daily dose (mg)	Annual costs
Amisulpride	400	£747	Chlorpromazine	300	£169
Aripiprazole	15	£1325	Haloperidol oral	8	£93
Clozapine	300	£964	Flupentixol decanoate	120 (per month)	£196
Olanzapine	10	£1036	Sulpiride	800	£263
Quetiapine	400	£1379	Trifluoperazine	20	£69
Oral risperidone	5	£1024	Zuclopenthixol depot	450 (per fortnight)	£175
Long-acting risperidone	25 (per fortnight)	£2162			

Relapse and PANSS

A patient history starts while the patient is in relapse. The duration of a relapse is drawn randomly from a predefined duration distribution that depends on patient profile and severity. Time between relapses is drawn from another distribution, and depends on patient profile, severity, current treatment, and compliance [17,26,38–44]. The model keeps track of patients' PANSS scores, ranging from 30 (least severe) to 210 (most severe) [45]. During a relapse, the PANSS score is higher than between relapses. PANSS scores can decrease through natural recovery or by means of pharmacological treatment.

For total recovery patients, the PANSS score will drop to the same level after a relapse. For partial recovery patients, the between-relapse PANSS score will increase after each relapse [43]. The model first calculates a "base" PANSS score as if the patient is noncompliant, after which the PANSS is corrected for the treatment effect of the specific drug the patient is on. During relapses, atypicals are assumed to reduce base PANSS by 20% and conventionals by 10%. Such a difference between conventionals and atypicals was substantiated by several studies and meta-analyses [5,46–51]. Between relapses, atypicals were assumed to reduce PANSS by 5%, whereas conventionals were assumed not to reduce PANSS throughout this period [26].

Compliance

The treatment effect is mitigated by compliance, which in turn depends on treatment location and drug regimen. Patients are assumed to be more compliant in hospital than at home [52,53], while patients on a depot are assumed to be more compliant than patients on oral formulation [54–56]. Moreover, patients are assumed to be slightly more compliant on an atypical than on a conventional antipsychotic (see Table 1) [52,57,58]. Finally, based on expert opinion, it was assumed that patients are 5% less compliant during relapse than between relapses.

The model first determines whether a patient is compliant or not, based on the aforementioned variables. If a patient is noncompliant, the model subsequently determines whether the patient is compliant (totally noncompliant, 60%) or partially noncompliant 40% during that period [58]. The impact of treatment in partially noncompliant patients in terms of PANSS reduction is put at 50% and the effect on time between relapses is halved as well. The impact of treatment in fully noncompliant patients is zero.

Quality of Life

A patient's quality of life (i.e., utility index) is derived from his/her PANSS score and the presence of side effects. The association between PANSS and utility is estimated on the basis of the relation found by Lenert et al. [35]. To estimate the impact of the different side effects, a multiplicative model is being used, where the parameters associated with weights gain are 0.959 [35], with tardive dyskinesia 0.857 [35], with diabetes 0.81 [59,60], with EPS 0.888 [35], and with sedation/somnolence 0.905 [61]. EPS and sedation/somnolence are assumed to exist as long as the medication is prescribed which caused it. Weight gain, tardive dyskinesia, and diabetes were assumed to last for the remainder of the time that the patient was included in the model, based on the more enduring nature of these side effects.

Costs

The annual cost per medication is calculated using data from the British National Formulary [62] and the Defined Daily Dosages, as reported by the WHO (see Table 2) [62]. The costs of the different care settings were retrieved from the Unit Costs of Health and Social Care Report 2006 (£96 psychiatrist visit [per patient contact of half an hour], £56 per fortnight for community care, £112 per week for intensive community care, £443 per week for a staffed hostel for patients with mental health problems, and £181 per day for psychiatric hospital care) [63].

The main outputs of the model are the predicted incremental discounted costs (expressed in £ per patient) and effects (expressed in QALYs per patient) after 5 years for atypicals compared to conventionals. Using these differences in cost and effect, the incremental cost-utility ratio (ICUR) of the atypicals was calculated (expressed as the cost per QALY gained). Besides QALYs, the effect outcomes also include information concerning symptoms, the number and duration of

relapses, and the amount of time spent in different treatment locations or on different treatments.

The influence of the uncertainty surrounding parameter estimates (i.e., second-order uncertainty) on the results is assessed using a probabilistic multivariate sensitivity analysis (or Monte Carlo simulation) and several deterministic univariate sensitivity analyses.

Pert, beta, lognormal, and uniform distributions were used to describe the second-order uncertainty of relevant variables (Table 3). Different distributions were used for different variables based on variable characteristics [64]. For the variables for which the level of uncertainty was unknown, uniform or Pert distributions were used. Such distributions allow for the specification of a fixed minimum, maximum, and most likely value [64].

Based on the costs and effects generated from 1000 cohorts of 10,000 patients, a cost-effectiveness scatter plot and acceptability curves were constructed [65]. The scatter plot is an illustration of the uncertainty surrounding the central estimate of the ICUR. Acceptability curves summarize the uncertainty associated with the decision to adopt a new treatment strategy for different willingness-to-pay (WTP) thresholds per QALY gained.

In order to investigate the effect of individual parameters on the outcomes generated in the probabilistic sensitivity analysis (incremental QALYs and incremental costs), an ordinary least squares (OLS) regression analysis was performed. This regression is performed using the inputs and incremental costs and effects from all 1000 cohorts.

Table 3 Overview of included uncertainty of model input parameters

Variable		Base case	Distribution	Parameters
Time between relapses [70]		Weibull beta atypicals	Normal	SE = 1.75
		Weibull beta conventionals (see Table 1)	Normal	SE = 1.72
PANSS		See Table 1 for different patient groups	Pert*	Min = +10% Max = −10%
Difference in PANSS reduction atypicals vs. conventionals	During relapse	10% in favor of atypicals	Pert*	Min = −0.05 Max = 0.25 ML = 0.10
	In between relapses	5% in favor of atypicals	Pert*	Min = −0.05 Max = 0.15 ML = 0.05
QALY [35]		$\beta_0 = 1.103$ $\beta_1 = -0.0043$	Normal*	SE = 0.11 SE = 0.00043
Risk†		$\beta_0 = -5.13$ $\beta_1 = 0.0403$	Normal	SE = 1.22 SE = 0.016
Patient profile [17]		Share of partial recovery patients (0.62)	Beta*	Alpha = 52
Severity		Percentage medium severe = 80%	Pert*	Beta = 32 Min = 70% Max = 90% ML = 80%
Duration hospitalization		Mean = 40	Normal*	SE = 3.4
Switching care setting probabilities		Probability hospitalization (Table 1)	Uniform*	Min = −15% Max = +15%
Side-effect probabilities		Base-case probabilities (Table 1)	Normal‡	SD = 25% of base-case estimate
Utility weight side effects [35,59,61]		Weight gain: 0.959 TD: 0.857 EPS: 0.888 Sedation: 0.905 Diabetes: 0.81	Normal	SD = 0.0102 SD = 0.0163 SD = 0.0168 SD = 0.0184 SD = 0.0133*
Probabilities to switch treatment because of side effects		Base-case probabilities (Table 1) were multiplied by:	Uniform*	Min = 0.9 Max = 1.1
Shortened time between episodes because of noncompliance		3.3 for conventionals 3.7 for atypicals	Pert*	Min = −10% Max = +10% ML = 3.32/3.7
Care setting costs [84]		See section 0	Lognormal*	SE = 10%
Difference compliance atypicals and conventionals		5% in favor of atypicals	Pert*	Min = 0% Max = 10% ML = 5%
Probability partial compliance [38]		If noncompliant: 40% partially noncompliant	Pert*	Min = 0% Max = 100% ML = 40%
Alpha weight (α) for PANSS in DCI		0.5	Uniform*	Min = 0.4 Max = 0.6

*For the distributions marked with an asterisk, the shape and interval of the uncertainty distribution were not available in the literature and are assumed, based on parameter characteristics and the level of uncertainty that existed among the experts.
†From B.M.S. Heeg, unpubl. ms.
‡For the side-effect incidence rates, not all confidence intervals were available. For all side effects, a normal distribution with a large SE of one-sixth (16.7%) of the base-case estimate was assumed.
DCI, disability to care index; EPS, extrapyramidal symptoms; ML, most likely; SE, standard error; TD, tardive dyskinesia.

Table 4 Overview of base-case cost and effect outcomes and incremental cost-effectiveness ratios for starting with a conventional or with an atypical

		Conventional group	Atypical group	Difference
Discounted costs (by cost component)	Community care	£4,282	£4,349	£67
	Intense community care	£3,541	£3,587	£46
	Staffed hostel	£14,710	£14,462	–£248
	Hospital	£30,072	£27,343	–£2,730
	Drug costs (incl. depot cost)	£3,588	£4,846	£1,258
	Psych visits	£3,349	£3,322	–£27
Undiscounted costs (over time)	Year 1	£14,156	£14,082	–£75
	Year 2	£11,376	£11,135	–£241
	Year 3	£12,893	£12,313	–£580
	Year 4	£12,519	£12,097	–£422
	Year 5	£12,858	£12,389	–£469
	Total discounted	£59,541	£57,908	–£1,633
QALY	Discounted 5-year total	3.53	3.64	0.10
Percentage of time spent per location	Community care	63.3%	64.3%	1.0%
	Intense community care	13.1%	13.3%	0.2%
	Staffed hostel	13.8%	13.6%	–0.2%
	Hospital	9.7%	8.8%	–0.9%
Percentage of total cost spent per location	Community care	7.2%	7.5%	0.3%
	Intense community care	5.9%	6.2%	0.2%
	Staffed Hostel	24.7%	25.0%	0.3%
	Hospital	50.5%	47.2%	–3.3%
Discontinuation of first treatment	Time on Tx1 (years)	1.36	1.51	0.15
	% still on Tx1 after 1 year	66.5%	72.4%	5.9%
Relapses	Number of relapses	2.67	2.64	–0.03
	Total relapse time	2.31	2.27	–0.03
Average PANSS	5-year total	62.7	59.8	–2.9

PANSS, Positive and Negative Symptom Score; QALY, quality-adjusted life-year.

Scenario Analyses

The NICE schizophrenia guidelines suggest the use of atypical antipsychotics for the early treatment of schizophrenia. This suggestion has been based on the evidence that atypical antipsychotics cause fewer EPS. In the base case of the model, three additional differences between atypicals and conventionals have been included based on literature. These differences concern a difference in compliance [66,67], in time between relapses [26,39,42], and in PANSS reduction [5,50,51]. To investigate the impact of these various differences on the model's results, four model runs have been carried out in a stepwise procedure. In the first run, only the difference in side-effect profiles between atypicals and conventionals is included. In consecutive runs, in a stepwise manner the differences in compliance, the time between relapses and in PANSS reduction are included.

Results

The base-case estimates of costs and effectiveness outcomes are summarized in Table 3. Starting with atypicals rather than conventionals was predicted to result in cost savings of £1633 (~3% of total costs). Drug costs increase by £1258, while hospital costs decrease by £2730. Hence, the reduction in hospitalization compensated for the higher cost of the atypical medications. It is expected that the atypicals on average avoid 16 hospital days per patient over 5 years. Table 4 shows that compared to conventionals, atypical drugs were predicted to reduce PANSS scores, increase time on first treatment, and improve quality of life. Thus, conventional antipsychotic treatment appeared to be dominated by atypicals because the latter were associated with cost savings (of £1633) and QALY gains (of 0.10). At a WTP of £30,000 per QALY gained, the expected incremental net benefit ($INB = \Delta E^{*}WTP - \Delta C$) of the atypical treatment arm was £4668 per patient over a 5-year period.

Average time on first treatment was 1.36 years on conventionals and 1.51 years on atypicals. After 5 years, about 70% of patients had experienced three treatment switches and were on clozapine treatment. Additionally the atypicals were expected to slightly reduce the number of relapses suffered (by 0.03 relapses over 5 years). This reduction in the average number of relapses realized by atypicals was smaller than expected because of the comparatively high proportion of patients on conventional depots in the UK (and thus relatively high compliance).

The uncertainty surrounding the cost per QALY gained is presented using a cost-effectiveness scatter plot (Fig. 3a). The center of the cost-effectiveness "cloud" lies below the *x*-axis, which indicates cost savings, and to the right of the *y*-axis, which implies health benefits at the same time. The information contained in the scatter plot is used to produce the acceptability curve (presented in Fig. 3b). This curve presents

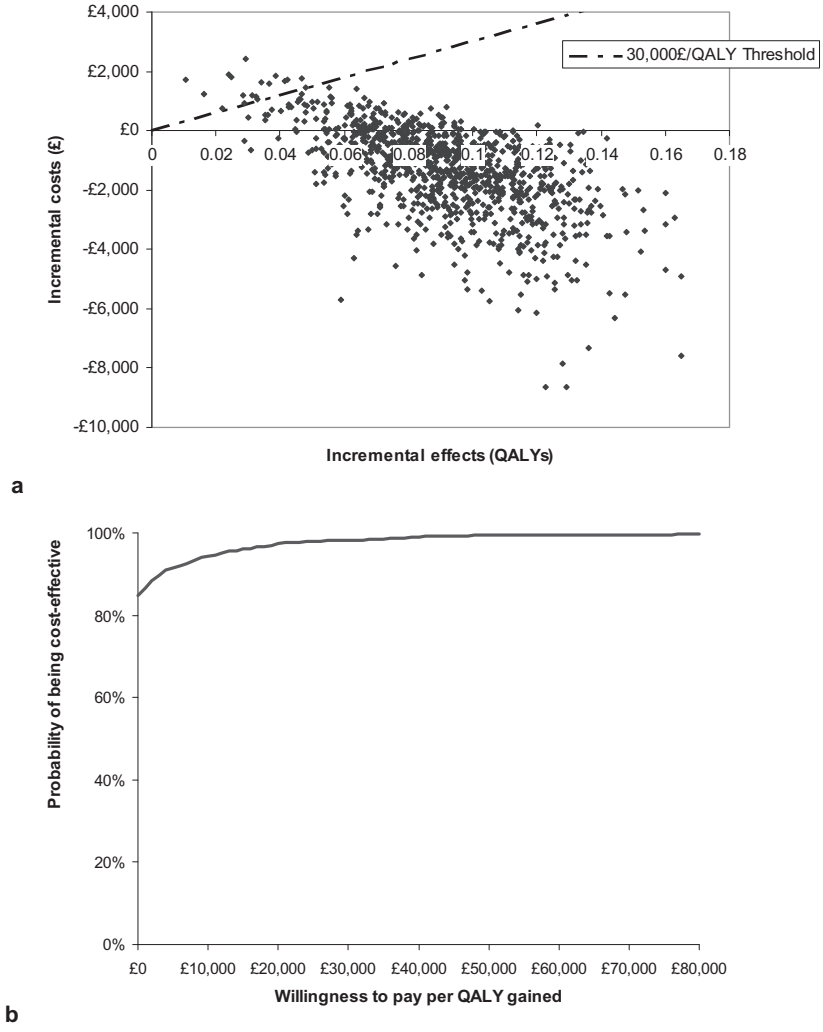

Figure 3 (a) Scatter plot of incremental costs and quality-adjusted life-years (QALYs) based on a 1000 runs of 10,000 patients. The larger portion of the scatter plot is found underneath the £30,000/QALY threshold, suggesting that treating patients with atypicals is likely to be cost-effective at the National Institute for Health and Clinical Excellence threshold of £30,000/QALY. (b) Acceptability curves: the probability that the new treatment option is cost-effective given various WTP thresholds for a QALY gained.

the probability of the "experimental" treatment being cost-effective compared to its comparator for various WTP thresholds, which are presented on the *x*-axis. In the UK, there is general consensus among policy-makers that a WTP threshold for a QALY gained of approximately £30,000 is acceptable [8]. At this threshold, with the given levels of uncertainty, the probability of atypicals being cost-effective compared to conventionals is 98.2%.

In Table 5, all variables are presented, which in the OLS analysis had a significant impact (P-value < 0.05) on incremental costs and/or effects that were generated in the multivariate sensitivity analysis. These variables have been sorted in descending order of their impact on the incremental outcomes. The last three columns of the table provide information about the influence of the worst case values. The values of the worst case and base-case values for a variable have been reproduced in columns 4 and 5. The product of the difference between these values multiplied by the regression coefficient is presented in column 6.

The results in Table 5 (part A) demonstrate that incremental costs were sensitive to changes in the values used of the parameters associated to whether or not the patient was at risk. Differences in the risk regression transformed the difference in PANSS reduction between conventionals and atypicals into a difference in hospitalization costs. Also, the difference between conventionals and atypicals in terms of PANSS reduction, compliance, and time between relapses had a significant impact on incremental costs.

From Table 5 (part B), it can be concluded that incremental effects are most sensitive to changes in the parameters of the QALY–PANSS relationship and the utility weights used in the calculations. The coefficients for EPS, tardive dyskinesia, and sedation were negative, because atypicals reduced these side effects, while coefficients hold for weight gain and diabetes, which are side effects more common in patients on atypicals. Side effects, especially those associated with serious consequences for quality of life such as tardive

Table 5 Regression analysis of incremental costs and effects (QALY) based on 1000 runs

Variables	Estimate	*P*-value	BC	Worst case	New ΔC BC = −£1633
A. Incremental costs regression					
PANSS reduction on atypicals (relapse)	15,090	0.000	0.80	0.93	£435
PANSS-risk regression beta 0	−1,197	0.000	−5.131	−6.802	£368
PANSS-risk regression beta 1	−121,400	0.000	0.0403	0.0299	−£366
Days in hospital	−35	0.000	40	13	−£668
Hospital location cost	−0.04	0.000	63,350	42,391	−£887
Compliance rate between relapses community treatment atypical oral	−3,361	0.000	0.65	0.43	−£907
PANSS episode partial recovery patients	−125	0.000	47.0	42.5	−£1,067
Compliance rate during relapses community treatment atypical oral	−2,153	0.000	0.60	0.40	−£1,210
PANSS reduction on atypicals (TBR)	4,371	0.000	0.95	1.044	−£1,220
Compliance rate between relapses community treatment conventional oral	2,104	0.000	0.60	0.79	−£1,235
Percentage partial recovery patients	−2,324	0.000	0.62	0.45	−£1,236
Compliance rate during relapses community treatment conventional oral	1,562	0.000	0.55	0.72	−£1,375
Probability of switching because of somnolence	987	0.007	0.30	0.51	−£1,425
Percentage of nonsevere patients	710	0.041	0.10	0.33	−£1,468
Shortening of TBR because of noncompliance atypicals	412	0.001	3.70	4.05	−£1,489

Variables	Estimate	*P*-value	BC	Worst case	New ΔE BC = 0.101
B. Incremental effects regression*					
PANSS Reduction on atypicals (relapse)	−0.306	0.000	0.80	0.93	0.059
QALY–PANSS regression beta	−7.363	0.000	−0.0043	−0.0023	0.086
Utility score EPS	−0.253	0.000	0.89	0.95	0.086
Incidence weight gain olanzapine	−0.034	0.000	0.41	0.78	0.088
Utility score weight gain	0.390	0.000	0.96	0.93	0.089
Incidence EPS flupentixol depot	0.028	0.000	0.58	0.17	0.089
Compliance rate between relapses community treatment atypical oral	0.051	0.000	0.65	0.43	0.090
PANSS reduction on atypicals (TBR)	−0.109	0.000	0.95	1.04	0.091
Percentage partial recovery patients	0.056	0.000	0.62	0.45	0.091
Compliance rate during relapses community treatment atypical oral	0.048	0.000	0.60	0.40	0.092
Incidence somnolence olanzapine	−0.030	0.000	0.30	0.59	0.092
Incidence somnolence quetiapine	−0.020	0.000	0.55	0.93	0.093
Zuclophentixol depot EPS	0.020	0.000	0.58	0.19	0.093
Utility score somnolence	−0.123	0.000	0.91	0.97	0.094
Incidence EPS haloperidol oral	0.017	0.000	0.58	0.14	0.094
Utility score TD	−0.149	0.000	0.86	0.91	0.094
Incidence somnolence flupentixol depot	0.020	0.000	0.49	0.14	0.094
Probability of switching after side-effect EPS	−0.037	0.000	0.30	0.48	0.094
Incidence EPS olanzapine	−0.043	0.000	0.16	0.30	0.095
Incidence EPS risperidone oral	−0.026	0.000	0.27	0.49	0.095
Incidence somnolence risperidone oral	−0.024	0.000	0.27	0.50	0.096
Incidence somnolence amisulpride	−0.019	0.000	0.27	0.54	0.096
PANSS episode partial recovery patients	0.001	0.000	47	42	0.096
Probability of switching after side-effect somnolence	−0.024	0.000	0.30	0.51	0.096
Incidence weight gain quetiapine	−0.020	0.000	0.33	0.58	0.096
Compliance rate during relapses community treatment conventional oral	−0.028	0.000	0.55	0.72	0.096
Incidence somnolence haloperidol oral	0.013	0.000	0.49	0.16	0.097
Incidence EPS trifluoperazine	0.010	0.000	0.58	0.14	0.097
Incidence TD flupentixol depot	0.122	0.000	0.05	0.02	0.097
Incidence EPS amisulpride	−0.012	0.000	0.33	0.65	0.097
Incidence EPS chlorpromazine	0.016	0.000	0.33	0.08	0.097
Incidence somnolence sulpiride	0.010	0.000	0.49	0.13	0.097
Incidence TD zuclophentixol depot	0.104	0.000	0.054	0.019	0.097
Compliance hospital atypical oral	0.011	0.000	0.80	0.45	0.097

*For the incremental effects OLS, a total of 67 parameters were found to be significant, only 34 are shown here. The remaining 33 did not lower incremental effects by more than 0.03 (i.e., New ΔE ≥0.098). Most of the parameters that were omitted deal with the incidence of side effects on the different treatments, and compliance rates in the different locations.

BC, base case; EPS, extrapyramidal symptoms; PANSS, Positive and Negative Symptom Score; QALY, quality-adjusted life-year; TBR, time between relapses; TD, tardive dyskinesia.

dyskinesia and diabetes, evidently had an important influence on incremental effects. In terms of effect size, the worst case value for the difference in PANSS reduction between atypicals and conventionals during episodes had the greatest impact on the incremental QALYs.

Scenario Analyses

Table 6 presents the cumulative nature in which the mechanisms which are made explicit in the model affect incremental costs, effects, and the ICUR. The more the model incorporates specific advantages of atypicals, the higher the incremental effects of the

Table 6 Sensitivity analysis: Analysis of the influence of the assumed differences between conventionals and atypicals

Included differences	Incremental costs	Effects	ICUR
Side effects only	£1,917	0.042	£45,205
+ Compliance	£1,695	0.046	£36,699
+ Time between relapses	£845	0.048	£17,778
+ PANSS reduction	−1,633	0.101	Dominant

ICUR, incremental cost-utility ratio; PANSS, Positive and Negative Symptom Score.

atypicals are and the lower incremental costs are. When assuming, similar to the NICE recommendations, only differences in the side-effect profiles of both types of antipsychotics, the ICUR is £45,205/QALY gained.

Discussion

The aim of this study was to assess the cost-utility of atypical antipsychotics in the treatment of schizophrenia compared to conventionals in the UK. On the basis of our calculations, it can be concluded that starting treatment of schizophrenia with an atypical instead of a conventional is associated with cost savings and with improved quality adjusted health over a 5-year period. Sensitivity analyses have shown that this conclusion of cost-effectiveness was quite robust to changes in input variables. The probabilistic analyses showed that atypicals will be cost-effective in a society where the WTP for a QALY is £30,000.

Our model calculations provide support for the NICE treatment guidelines which suggest that atypical antipsychotics should be considered for the first-line treatment of schizophrenia [4]. This confirmation is not unequivocal. The argumentation behind the NICE recommendation relied mainly on EPS being avoided by atypicals compared to conventionals, while in the base case the model included additional differences that are believed to exist between the treatments. The scenario analysis which reflects the NICE recommendation, i.e., assumes only differences in side effects between atypicals and conventionals, indicates that the use of atypicals would be associated with an ICUR of approximately £45,000/QALY. This ICUR decreases dramatically if a difference in compliance, the time between relapses and PANSS reduction, is also assumed to a dominant ICUR in the last scenario, which is also the base case.

The debate in the literature of the cost and effects of atypicals and conventionals is inconclusive [5,14,39,46–51,68–73]. For instance recently, Jones et al. concluded that in people with schizophrenia whose medication is changed for clinical reasons that there is no disadvantage across 1 year in terms of quality of life, symptoms, or associated costs of care in using conventional antipsychotics rather than atypical antipsychotics (nonclozapine) [69]. Moreover, in a 12-month study, Rosenheck et al. found that olanzapine demonstrated no advantages over haloperidol (with prophylactic benztropine against EPS) in compliance, symptoms, EPS, and quality of life [74]. Furthermore, Lewis et al. argue that conventional antipsychotic drugs still have a place in the treatment of patients unresponsive to, or intolerant of, current medication [75]. Kane et al. and Mahmoud et al. however, found that clinically relevant quality of life gains were more frequent with an atypical than with a conventional antipsychotic [70,71]. Further, Schooler et al. also showed that the time between relapses is longer on risperidone than on haloperidol [39]. The length of study, the choice of (conventional) comparator (and potential concomitant treatments), patient selection, dosing used, outcome measures used, and the trial setup may explain this variation in the evidence [5,74,76].

The version of the model used for the current article was an upgrade of an earlier one [11–13]. This version of the model is suitable to carry out second-order Monte Carlo simulation and therefore has the capacity to investigate uncertainty across populations rather than across individuals. This is important because reimbursement decisions have to be taken on the basis of uncertainty around incremental cost-effectiveness ratios at the population level. NICE guidelines [64] indicate that such a probabilistic analysis is mandatory for all applications to be evaluated by NICE.

As much as was feasible, data from the literature have been used in the model calculations. Nevertheless, because of the lack of long-term data in schizophrenia, it is still unavoidable to make a few assumptions which have been substantiated by expert opinion. Therefore, predicted costs per patient, treatment location, and disease progression were compared with published sources. The modeled PANSS scores over time reflected the observations from Mahmoud et al. [70] and from the ongoing University Medical Center Utrecht cohort study at model entry and after 1 and 5 years, respectively. The average patient in the model was in relapse for 27.7 months over 5 years, which was 46% of the modeled 5 years. This is in line with the findings from Mason et al. [77] and Lenoir et al. [78]. Compared to that of Knapp et al., the probability in the model to be treated in a certain treatment setting appeared to be modeled quite conservatively with the average patient spending approximately 78% of time in the community (of which 15% in intense community care), 14% in a staffed hostel, and 8% in hospital (in the conventional treatment arm) [79]. The shift from hospital to community care reflects efforts that have been made since Knapp's publication to reduce the number of long-term psychiatric inpatients. Additionally, similar to Guest and Cookson, the total annual (undiscounted) direct care costs in the model were estimated at approximately £10,000 per patient

[80]. The model predicted that time on first-line treatment was about 15% longer for atypicals than for conventionals. These differences were also found in a large observational study [81], but not in CATIE [14].

Finally, with respect to the variables differing between the conventionals and the atypicals, the individual drugs within the group of atypicals and within the group of conventionals were assumed to have an identical effect. This was necessary because relevant comparative studies between the different atypicals were not available. A number of sources suggest that some differences do exist between individual drugs. Tiihonen et al., for example, found significant differences in the incidence of relapses between different atypical and conventional drugs in an observational study, even when corrected for patient characteristics [82]. Further research into any efficacy differences that might exist between individual drugs is needed to test this assumption, which can then be incorporated into the model together with more detailed drug-specific cost-effectiveness estimates.

Conclusion

According to this DES model for schizophrenia, atypical antipsychotics are cost-effective compared to the conventional antipsychotics. The assumptions used in the model need further validation through large naturalistic based studies with reasonable follow-up to determine the real-life differences between atypicals and conventional antipsychotics.

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Supplemental materials for this article can be found at: http://www.ispor.org/publications/value/ViHsupplementary.asp

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Appendix A: Disability to Care Index

The treatment setting assigned to a patient depends on the level of self-care ability. This level is operationalized using the disability to care index (DCI), which in turn depends on the patient's PANSS and social and environmental factors (SEFs). The DCI ranges from 0 to 10 and patients are classified into three levels of self-care ability (able to care, moderately able to care, not able to care) according to prespecified DCI thresholds. This classification of a patient's self-care ability plays an important role in the treatment location decision made by the psychiatrist.

The formula used to calculate DCI is the following:

$$DCI = \frac{\alpha \times SEF + (1-\alpha) \times PANSS_{\text{trans}}}{10}$$

Where α is the SEF weight, and $PANSS_{\text{trans}}$ is a patient's PANSS scores transformed from its usual range (30–210) to a range from 0 to 100 using a cumulative normal distribution. This shape was chosen in order to ensure sensitivity over the relevant PANSS range while still being able to deal with all possible PANSS scores.

Figure 4 shows the relationship between PANSS and DCI, and the influence of α. With an α of 0 (the blue circles) only PANSS influences DCI. With an SEF weight of 0 (the green diamonds), patients have an average DCI of 5, independent of their PANSS score. With an $\alpha > 0$ SEFs have, on average, a diluting effect on the influence of PANSS on the disability index and thus location (e.g., the red diamonds, with an α of 0.5).

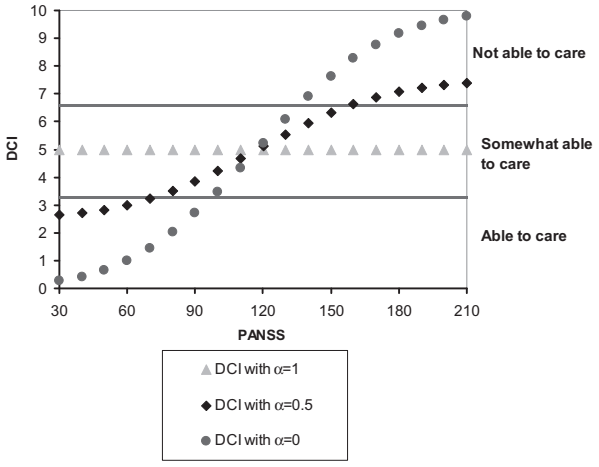

Figure 4 Disability to care index (DCI) against Positive and Negative Symptom Score (PANSS) for different α-weights.